IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 10/802,220

Confirmation No. 3562

Applicant: Sunami et al.

Filed: March 17, 2004

TC/AU: 1614

Examiner: Pagonakis, A.

Docket No.: 227833

Customer No.: 23460

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the following sheets.

Respectfully submitted,

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Date: January 15, 2009

REMARKS/ARGUMENTS

Status of Claims

Claims 1-8 and 15-23 are pending and are the subject of this appeal.

Summary of Claimed Subject Matter

Claims 1-8 are directed to a pharmaceutical composition comprising (i) *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate (hereinafter "JTT-705") and (ii) crospovidone (see, e.g., specification paragraphs 0015, 0075, and 0088). Claims 15-23 are directed to a method of treating a cardiovascular disorder with the aforementioned pharmaceutical composition (see, e.g., specification paragraph 0101).

Grounds of Rejection to be Reviewed

Claims 1-8 and 15-23 are rejected under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. (U.S. Patent Application Publication 2006/0014788) in view of Ault et al. (U.S. Patent 7,049,283) and Englert et al. (U.S. Patent 6,723,751).

Claims 1-8 and 15-23 have been rejected for nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. II (U.S. Patent 6,753,346) in view of Ault et al. (U.S. Patent 7,049,283).

Reasons for Withdrawal of Rejections

A. Obviousness Rejection

The Office has failed to establish a *prima facie* case of obviousness because the Office has not pointed to anything in any of the cited references to indicate *why* one would combine the two disclosures. Applicants maintain that nothing in either of Gumkowski et al., Ault et al., or Englert et al. would lead one of ordinary skill in the art to arrive at the *specific* composition or method of the pending claims that require (a) a pharmaceutical composition comprising JTT-705 and crospovidone (e.g., claim 1), (b) a pharmaceutical composition comprising (i) substantially crystalline JTT-705, in which the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive (e.g., claim 5), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising JTT-705 and crospovidone (e.g., claim 15).

As the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v.*

Teleflex Inc., 127 S. Ct. 1727, 1741, 82 U.S.P.Q.2d 1385, 1396 (2007) (emphasis added)). With respect to the present application, the Office has failed to articulate any reasoning with a rational underpinning to support the obviousness rejection in view of Gumkowski et al., Ault et al., and Englert et al.

Firstly, Gumkowski et al. discloses *hundreds* of disparate CETP inhibitors – only one of which is JTT-705 (see paragraphs 0113-1035). There is no pointer in Gumkowski et al. to JTT-705 specifically. Ault et al. discloses the use of crospovidone but is not directed to the use of CETP inhibitors *at all* or the treatment of cardiovascular disorders. Englert et al. discloses the crystallization of a compound with a chemical structure that is quite different from that of JTT-705. In view of the unrelatedness of the disclosures of these references to each another, one of ordinary skill in the art would not be led to the combination of these references in the first place. In other words, if one had no prior knowledge of Applicants' invention, that ordinary artisan would not come to the conclusion that the disclosures of Gumkowski et al., Ault et al., and Englert et al. *should* be combined. To assert otherwise, ignores the unrelatedness of the cited references to each other and relies on improper and impermissible hindsight knowledge of Applicants' invention. See, e.g., *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."); see also *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983) (warning of the danger of "fall[ing] victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

As further evidence of the unobviousness of the present invention, Ault et al. describes agents that "do not pass or which pass only a small amount of the administered dose through the gastro-intestinal mucosa and/or are susceptible to cleavage by acids and enzymes in the gastro-intestinal tract" (col. 2, lines 43-49). Ault et al. contends that an additive such as crospovidone or povidone will maintain the integrity of these agents susceptible to cleavage, thereby increasing their bioavailability. This teaching in Ault et al. constitutes a teaching away from using an additive such as crospovidone in a formulation comprising a compound, such as JTT-705, that *must* cleave *in vivo* to form an active agent.

In particular, JTT-705 *must be* hydrolyzed *in vivo* to form the active agent (see the specification at, e.g., paragraph 0076). As a result, even if it were assumed that one would knowingly select JTT-705 from Gumkowski et al. and then seek out additional references for teachings on how to increase the bioavailability of JTT-705, that ordinary artisan would not rely upon the disclosure of Ault et al. because Ault et al. teaches that crospovidone will prevent a compound from cleaving *in vivo*.

With respect to claim 2, the Office contends that Gumkowski et al. discloses that the CETP inhibitor can be provided in a formulation in an amount of 1-50 wt%, which meets the limitation requiring that more than 50% of the CETP inhibitor is crystalline (Office Action issued October 15, 2008, page 5, second paragraph). Applicants fail to understand how Gumkowski et al.'s disclosure that a composition can include a CETP inhibitor *in an amount of 1-50 wt%* meets the limitation in claim 2 in which *more than 50% of the CETP inhibitor is crystalline*. Gumkowski et al. does not teach or suggest an embodiment in which at least 50% of *any* of the CETP inhibitors described therein are crystalline, let alone JTT-705, as required by claim 2.

As regards claims 2-6, the Office alleges that it would have been obvious to use the crystallization techniques of Englert et al. because Englert et al. teaches a benzamide structure. Applicants have pointed out that the compounds of Englert et al. and the pending claims are structurally unrelated to one another except that both compounds happen to contain a benzamide moiety (see Response to Office Action submitted July 15, 2008, pages 11-12). The Office maintains that "given that the crystallization of benzamides (as stated above) is capable one would also be motivated to crystallize any benzamide" (Office Action issued October 15, 2008, page 4, bottom paragraph). Given the disparate chemical structures, the mere presence of a benzamide group in JTT-705 would not cause one of ordinary skill in the art to reasonably believe that the crystallization technique disclosed in Englert et al. could be applied with success to JTT-705. However, even if one were to assume that based on the disclosure of Englert et al. that another benzamide-containing compound could be crystallized, this information does not surmount to the specific features recited in claims 2, 3, and 5. In particular, nothing in Englert et al. (nor Gumkowski et al. or Ault et al.) teaches or suggests providing JTT-705 in a specific crystalline or amorphous amount.

The Office states that "Applicant's arguments fail to clearly point out the patentable novelty which he thinks the claims present in view of the state of the art disclosed by the

reference cited" (Office Action issued October 15, 2008, page 5, bottom paragraph). However, contrary to the Office's assertion, the pending claims define novel subject matter as demonstrated by the fact that no anticipation rejection has been made by the Office.

B. Obviousness-type Double Patenting Rejection

An obviousness-type double patenting rejection is only proper when the pending claims of an application recite an obvious variation of the invention that is *claimed* in a patent or patent application (MPEP § 804.II.B.1). The *specification* of the relied upon patent or patent application – here, Shinkai et al. II – is not involved in such an analysis. However, contrary to this standard, the Office states, "[i]t is obvious from the above teachings of [the] '346 patent that it expressly contemplates variation in the dosage amounts and schedule of the active agents" (Office Action issued October 15, 2008, page 7, first full paragraph). Applicants note that while the *specification* of Shinkai et al. II discloses administration information about JTT-705, the *claims* of Shinkai et al. do not "expressly contemplate variation in dosage amounts and schedule of the active agents," as alleged by the Office.

Shinkai et al. II contains *claims* directed to JTT-705, a composition thereof, and methods of use thereof. The *claims* of Shinkai et al. II do not teach or suggest (a) a pharmaceutical composition comprising JTT-705 *and crospovidone* (e.g., claim 1), (b) a pharmaceutical composition comprising (i) substantially crystalline JTT-705, in which the amount of inhibitor in amorphous form does not exceed about 10% and (ii) *a water-insoluble concentration-enhancing additive* (e.g., claim 5), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising JTT-705 *and crospovidone* (e.g., claim 15), as recited in the pending claims. Since the *claims* of Shinkai et al. II do not teach or suggest a pharmaceutical composition comprising a water-insoluble concentration-enhancing additive, such as crospovidone, the Office relies on the disclosure of Ault et al.

However, upon considering the *claims* of Shinkai et al. II, one of ordinary skill in the art would not know that there existed a need to increase the bioavailability of JTT-705 and as such would not know to seek another reference, let alone Ault et al. Again, the Office uses an improper hindsight analysis to assert that one would know to search the literature and arrive at the disclosure of Ault et al., which is *not* directed to the use of CETP inhibitors at all or the treatment of cardiovascular disorders.